NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2004

PLAN FOR HIV-RELATED RESEARCH

II: NATURAL HISTORY AND EPIDEMIOLOGY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Natural History and Epidemiology

SCIENTIFIC ISSUES

Epidemiologic research shows that the HIV/AIDS epidemic continues to evolve in the industrialized and developing world, albeit on different trajectories. In the middle and late 1990s, advances in HIV treatments widely available in the United States and other industrialized countries led to dramatic improvements, as shown by far fewer AIDS deaths and much slower progression rates of HIV-related disease. The rate of such declines in AIDS cases and AIDS deaths, however, has markedly slowed in recent times. In the United States, the composition of the epidemic also is changing, with increases in the number of new HIV infections in some groups, such as women, racial and ethnic minorities, adolescents, injecting drug users, and some segments of men who have sex with men. In addition, the long-term effects of potent antiviral therapies are becoming more obvious, with new and more frequent occurrences of adverse health effects and the related problems of drug discontinuation and drug resistance.

In developing countries, where the therapeutic advances of the industrialized world are not widely available, the epidemic has continued unabated, pointing to the urgent need for rigorous research that leads to the formulation of evidence-based interventions. NIH-sponsored research has been accelerating in areas severely affected by the epidemic, such as Africa, Asia, and the Caribbean, but a great deal more is necessary to increase the knowledge base about the epidemic characteristics in different geographic areas. In the developing world, basic epidemiologic studies on the rate of HIV and AIDS in different populations are being complemented by

systematic and integrated studies that quantify the separate but intertwined effects of viral, host, and environmental factors. Findings from epidemiologic research can be used to inform rational HIV prevention and treatment interventions in locales with diverse characteristics and needs.

PRIORITY FOR FUTURE RESEARCH:

- **Structure epidemiological studies in domestic and international communities to characterize risk factors for transmission and assess the impact of interventions (antiviral therapy, prevention programs, etc.) on HIV incidence, risk behaviors, and outcomes of infection in adult and pediatric populations.**

The five million new infections that occurred worldwide in 2001, the latest period for which global estimates are available, point to the continuing need for multidisciplinary research, including epidemiologic research, on HIV transmission. Epidemiologic studies are necessary to document rates of HIV transmission and related risk factors in populations that differ in multiple ways, including age, demographics, and sexual behaviors as well as biologic characteristics, such as host immune status, genetic make-up, and HIV subtype characteristics. In the face of an epidemic that continues to evolve, NIH-sponsored epidemiologic research permits scientists to quantify risks and exposures to specific risk factors and in specific populations. The assessment of the effect of interventions on new HIV infection rates and other related endpoints will be an important part of NIH epidemiologic studies on HIV transmission. Some interventions have profound impact on health status. This is exemplified by the impact of breast-feeding by HIV-infected women: studies are urgently needed to establish not only the role of breast-feeding in transmitting HIV infection, but also its role in infant survival and maternal health. Transmission studies need to be designed such that study findings can be applied to broader populations. In addition to the therapeutic benefits for individuals, the expansion of antiretroviral options in the developing world may result, through a lower HIV transmission rate, in a containment of the epidemic in some situations. Studies are needed, though, to assess whether the availability of antiretroviral therapies may lead to riskier sexual behaviors. The rigorous design of interventions and the assessment of their effectiveness constitute a high-level priority in order to control the spread of HIV.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and implement studies to provide epidemiologic data that will serve as the basis for intervention trials in domestic and international locales.**

In spite of continuing progress, there is still inadequate knowledge of HIV and host dynamics, as well as of environmental and behavioral factors, especially in the developing world. However, such knowledge is necessary to inform the design and conduct of experimental studies (i.e., randomized controlled trials of preventive or therapeutic interventions) on HIV/AIDS. Particularly relevant to this priority are studies that support the capacity of networks, such as the HIV Prevention Trials Network and the HIV Vaccine Trials Network, to advance the development of effective vaccines and other prevention approaches that may prevent infection or alter the HIV infection course.

At this stage of the global HIV epidemic, NIH-sponsored epidemiologic studies on HIV/AIDS should expand the knowledge of HIV disease and its prognostic indicators by clearly defining the key scientific questions that are relevant in specific geographic areas and the parameters that must be monitored to address those questions. Research areas that need emphasis and can profit from a rigorous epidemiologic approach include those focusing on the role of viral and host diversity in response to interventions, such as candidate HIV vaccines; quantification of the impact of introducing antiretroviral therapy on key clinical and laboratory outcomes; assessment of the merits of clinical and laboratory parameters and markers that might be widely used in clinical care and population screening; and approaches for selecting representative populations for therapeutic or preventive trials.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and evaluate accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; measures of adherence to therapy; and markers of recent infection for large-scale use in domestic and international settings.**

The understanding of HIV infection, disease progression, and effects of interventions rests in large measure on the development and the availability of valid and reproducible biological assays. Assays are needed to screen populations for HIV-related or host-related factors that directly affect the diagnosis, prognosis, and treatment of HIV/AIDS. Highly sensitive and specific assays are needed for the widespread diagnosis of HIV, opportunistic infections (OIs), cancers, and other HIV-related conditions. In addition, a broader array of assays is necessary to optimize prognosis and treatment by monitoring the efficacy and possible toxicity of antiretroviral therapies. As the use of such therapies becomes more widespread in the developing world, new assays will be needed that are simple, affordable, and have long shelf life under unfavorable environmental

conditions. Assays developed for early detection of subtype B HIV infection (the subtype present in North America and most of Europe) will need to be adapted to the early detection of HIV subtypes that are common in other regions of the world. NIH should emphasize research leading to the development and evaluation of high-quality assays, including assays that are suitable for large-scale screening use, monitoring of interventions, and clinical use in different situations and regions.

PRIORITY FOR FUTURE RESEARCH:

- **Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics. Use this approach to increase the understanding of natural history, treated history, and pathogenesis of HIV infection and disease, including adverse events in the presence of interventions.**

A constant effort must be made to adjust the NIH research effort on HIV/AIDS to the changing epidemic. In the United States, the epidemic, after affecting mainly white homosexual men in the 1980s, shifted in part in the 1990s to include new populations, such as women, drug users and their sexual partners, and racial and ethnic minorities. Internationally, individual subepidemics in different geographic regions and populations have arisen or expanded. A domestic and international infrastructure must be maintained and strengthened to study biologic and behavioral aspects of HIV/AIDS in new or previously understudied populations. In particular, long-term cohort studies have been recently emphasized for U.S.-based research as a scientifically appropriate and administratively effective means to investigate the rates and determinants of HIV disease progression, HIV pathogenesis, causes of death, and effects of therapy in modifying the spectrum of HIV-related disease. These studies, with appropriate modifications according to individual regions, can also be promoted in developing countries where NIH has been increasing the number and scope of HIV/AIDS research projects. Within such long-term studies of HIV/AIDS, NIH must also support the establishment or further development of key enabling tools, including repositories of biological specimens, standardization of study instruments, electronic data transfer, data sharing, and electronic dissemination of study findings. Enabling tools and technologies will increase the scope and quality of research findings and accelerate their dissemination, leading to a more rapid implementation of authentic research-based health measures.

PRIORITY FOR FUTURE RESEARCH:

- **Enhance our understanding of the interactions between the epidemiology, prevention, treatment, and management of HIV and concomitant infections and disorders. Investigate the implications of concomitant infections on immunogenicity and efficacy of HIV vaccine candidates.**

Many elements of illness—referred to as co-morbidities—in HIV-infected individuals are attributable to diseases other than HIV. HIV co-morbidities often affect the prognosis of HIV disease and its response to therapeutics. Identifying the role of co-morbidities in HIV-infected individuals is important because effective antiretroviral therapies, by prolonging life, increase the time over which co-morbid disease may occur and have been associated with severe long-term toxicities that may be exacerbated in the presence of co-morbidities. Co-morbid disease can have an infectious origin (e.g., hepatitis B and C) or a noninfectious origin (e.g., mental illness, alcohol and other substance abuse). In the developing world, concomitant infections with endemic pathogens and nutritional deficits may affect, directly or through co-morbid conditions, the successful use of antiretroviral regimens. In those geographic areas, NIH-sponsored studies are needed to follow heterogeneous populations and establish the mutual effects of HIV disease, co-morbidities, and their treatments. In addition, co-morbidities should be studied to establish whether they might negatively impact the immunogenicity and efficacy of HIV/AIDS vaccines candidates.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Characterize the risk factors and mechanisms of HIV transmission in domestic and international populations, to guide strategies for prevention of transmission.

STRATEGIES:

- Identify, establish, and maintain cohorts in which HIV transmission and acquisition can be assessed, including incident cohorts.
- Conduct studies on the molecular epidemiology and the effects on HIV transmission of infection with different HIV subtypes, antiretroviral resistance mutants, multiple subtypes, and recombinant virus.
- Evaluate sexual and blood-borne HIV transmission and acquisition in relation to the following:
  - Viral factors such as viral concentration (both RNA and proviral levels) in various body compartments (e.g., blood, mucosal compartments) and HIV genotype including subtypes, recombinants, resistance mutants, and dual virus infections;
  - Host factors such as age, sex, hormonal status, strength and breadth of immune response, mental health, and host genetic factors;
  - Modifiable host factors such as nutrition, substance (defined throughout this section to include alcohol, tobacco, and drugs—including "club drugs") abuse; other infections; other causes of mucosal pathology, including sexually transmitted diseases (STDs); and circadian rhythm;
  - Use of microbicides and barrier devices;
  - Social, cultural, behavioral, and ecologic factors, including such demographic characteristics as socioeconomic status, race, ethnicity, gender, culture, and community;
  - Sexual activity, duration of partnership, control of STDs, hygienic practices, contraception choices, and cultural practices such as use of traditional vaginal preparations, female genital mutilation, and male circumcision;
  - Health care issues, including access, quality, sustainability, and education for prevention; and

  - Extent to which environmental and other macro-level factors such as war, migration, drug trafficking patterns, and disasters influence vulnerability, risk behaviors, acquisition, and access to care in developed and developing countries.

- Evaluate the impact on HIV transmission of antiretroviral therapies, medication adherence, and related factors such as therapy and regimen characteristics, HIV incidence, drug effectiveness, symptom management, and impact of viral load suppression on patterns of risk behavior.

- Employ epidemiological techniques to evaluate and quantify the impact of different intervention strategies on HIV transmission and prevention.

- Evaluate risks, benefits, and cost-effectiveness of providing prophylaxis against HIV infection after occupational and parenteral exposures to HIV.

- Examine the effects of vaccine trials on HIV transmission characteristics, including the effects on the alteration of transmission by vaccine-induced immunity. Examine the clinical course and markers of infectiousness among vaccine trial participants with breakthrough HIV infection to determine the vaccine's effect on viral load, rates of progression, and on population HIV incidence.

- Conduct studies on medication-assisted substance abuse treatment modalities (e.g., methadone maintenance, buprenorphine/naloxone, naltrexone, and stimulant abuse therapy) alone or in combination with behavioral interventions as HIV prevention interventions.

- Identify effective individual, network, and community-level interventions and determine the coverage needed to prevent, arrest, and reverse HIV epidemics in developing and developed countries.

- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including infant feeding modalities, physiology of lactation, long-term effects of perinatal interventions, and kinetics of viral resistance.

  - Assess the impact of breast-feeding practices on mother-to-child transmission of HIV and on the health of children and mothers.

  - Assess the impact of maternal antiretroviral regimens on mother-to-child transmission of HIV.

- Assess the impact of postnatal antiretroviral therapy of children on mother-to-child transmission of HIV.
- Assess the impact of perinatal treatment and prophylaxis regimens on community-wide resistance to antiretrovirals.

OBJECTIVE - B:

Use epidemiologic research in domestic and international settings to identify the influence of therapeutic and other biologic (e.g., co-infections) and behavioral (e.g., access) factors on HIV progression, as shown by virologic, immunologic, and clinical outcomes.

STRATEGIES:

- Investigate the contribution of innate host characteristics on viral measures, immune function, disease progression, and mechanisms for these effects (including host genetic factors, sex, race, and age).
- Evaluate the effects of modifiable host characteristics on viral measures, immune function, disease progression, and mechanisms for these effects.
- Investigate the effect on disease progression of viral factors, including viral genotype, phenotype, and acquired drug resistance to antiretroviral drugs.
- Evaluate the impact of treatment of substance abuse and mental health disorders on the effectiveness of antiretroviral therapy.
- Identify the individual, provider, and structural factors associated with initiating, continuing, and discontinuing antiretroviral therapy.
- Characterize the changing spectrum of clinical outcomes (morbidity and mortality), including causes of death associated with evolving therapeutic strategies.
- Determine the global patterns of viral resistance (innate and acquired) to antiretroviral therapies and how these patterns could influence the long-term effectiveness of these therapies.
- Evaluate the rate of HIV disease progression in conjunction with the effects of feasible interventions (antiretroviral and other prophylactic) in international settings and in populations with different HIV subtypes and variable co-factors such as nutrition and OIs.
- Develop new cohorts and maintain long-term followup of existing cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of HIV disease and evaluate interventions, including indigenous approaches, especially in minority populations and developing countries. Emphasis should be placed on cohorts that allow for subgroup comparisons.

- Continue to characterize in adults and children the epidemiology of HIV infection and associated OIs or conditions among those who have minimal exposure to antiretroviral therapies, those who have virologic and/or immunologic responses to these therapies, and those who have failed these therapies.
- Evaluate the long-term complications of antiretroviral therapy on exposed, HIV-uninfected children.
- Examine the effect of the health status of HIV-infected mothers on survival of their children, both HIV-infected and uninfected.
- Identify the effects of long-term exposure to HIV therapies on other infectious diseases; malignancies and associated oncogenic infections; cardiovascular disease; and other HIV-associated diseases, including central and peripheral nervous system conditions, cardiovascular manifestations, oral and mucosal lesions, and wasting and other metabolic disorders.
- Elucidate the pathogenic mechanisms mediating HIV disease progression in well-defined population subgroups, including the factors that influence residual HIV replication in antiretroviral treatment recipients.
- Investigate how different patterns of access, adherence, and exposure to drug regimens in treatment-experienced and treatment-inexperienced populations contribute to HIV drug resistance and disease progression.
- Assess the effect of HIV on other infections (e.g., GB virus C [GBV-C or hepatitis G], hepatitis C [HCV], hepatitis B [HBV], human papillomaviruses, other blood-borne infections, tuberculosis, and malaria) and the effect of these infections on HIV outcomes.
- Study HIV-infected infants, children, and adolescents to determine factors related to divergent rates of disease progression, mechanisms that contribute to impaired growth and neurodevelopment, physical and emotional impact of other childhood infectious diseases, safety and efficacy of immunizations, childhood- and adolescent-specific complications, and the impact of medical and behavioral treatment interventions on the above.
- Study the effect of HIV infection and its treatment in aging populations with coexisting morbidities and polypharmacy.

- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections (e.g., multidrug-resistant tuberculosis, sulfa-resistant malaria, cotrimoxazole-resistant *Pneumocystis carinii* pneumonia [PCP], and lamivudine-resistant HBV) in HIV-infected populations.
- Study determinants of adherence to antiretroviral therapy, including the role of traditional approaches, and adverse events of such therapies in international settings.

OBJECTIVE - C:

Develop and evaluate methods and resources for epidemiologic and clinical studies to use culturally relevant approaches; to incorporate new laboratory, sampling, and statistical methods and information systems; and to better integrate research findings into policy and practice.

STRATEGIES:

- Evaluate and promote the use of study designs that incorporate appropriate cultural and policy context and ethical considerations for studies in diverse domestic and international populations.
- Determine how to best utilize existing or future observational studies and randomized controlled trials to answer outstanding research questions.
- Develop and evaluate accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, and genetic assays suitable for large-scale epidemiologic research and surveillance in developing nations. Emphasis should be on rapid HIV detection testing, staging disease progression for the initiation and monitoring of HIV therapy and OI prophylaxis, HIV resistance testing, validation of detuned assays, and noninvasive diagnostic assays for STDs, other OIs, and AIDS-related malignancies.
- Assess the impact of rapid diagnostic assays in conjunction with interventions to reduce mother-to-child transmission in different health care settings.
- Assess the effectiveness of clinical versus laboratory monitoring for the initiation and management of antiretroviral therapy, particularly in resource-poor settings.
- Develop new epidemiological designs and statistical methods to better characterize transmission dynamics and monitor long-term trends in disease progression in the era of potent antiretroviral therapy.
- Support a comprehensive, interdisciplinary methods research program on the design and analysis of clinical trials evaluating treatment strategies, multiple interventions, and composite endpoints.
- Develop innovative approaches to link records, in a manner respectful of study participant privacy, to facilitate better studies of HIV-associated diseases and mortality.

- Develop and evaluate methods to access, recruit, and retain, in biomedical and behavioral preventive intervention studies, at-risk populations such as minorities, children, adolescents, women, substance users, incarcerated populations, and persons living with mental illness in domestic and international settings.
- Develop, maintain, and effectively cultivate ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies. Nested studies that utilize these resources should be particularly encouraged and developed.
- Support studies that identify and evaluate the translation of relevant research findings into policy and practice.
- Support training and mentorship of medical and health professionals in developing countries in the areas of research ethics, study design, data management, and analysis.
- Study the impact of policy changes on risk behaviors, HIV acquisition, and access to health care among at-risk populations in developed and developing countries.
- Develop and evaluate counseling procedures for individuals receiving HIV-related prognostic and diagnostic tests and vaccine candidates.
- Develop, evaluate, and promote new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion and other iatrogenic exposures in developing countries, including instrument sterilization.
- Explore low-cost, low-technology interventions for curtailing HIV disease progression in developing countries, including structural interventions, nutritional interventions, and improved prophylaxis and treatment of OIs.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

FY 2004 OAR Planning Group for Natural History and Epidemiology

FY 2004 NATURAL HISTORY AND EPIDEMIOLOGY PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ARV	antiretroviral
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CFAR	Center for AIDS Research
CIPRA	Comprehensive International Programs for Research on AIDS
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
ddI	dideoxyinosine
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GBV-C	GB virus (hepatitis G)

GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria
GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium* complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission

N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization
NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NMAC	National Minority AIDS Council
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
OPHS	Office of Public Health and Science
PBMC	peripheral blood mononuclear cell
PCP	*pneumocystis carinii* pneumonia
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trial
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis

Th	T helper cells
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study
WRAIR	Walter Reed Army Institute for Research